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A prospective cohort study on consumption of alcoholic beverages in relation to prostate cancer incidence (The Netherlands)

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Abstract

Objectives: To examine alcohol consumption in relation to prostate cancer incidence in the Netherlands Cohort Study.
Methods: At baseline in 1986, 58,279 men aged 55–69 years completed a self-administered questionnaire on diet, consumption of alcoholic beverages and other risk factors for cancer. For data processing and analyses the case–cohort approach was used. After 6.3 years of follow-up, 680 incident primary prostate cancer cases were available for analysis.
Results: In multivariate analyses adjusted for age, socioeconomic status and family history of prostate cancer, no association between total alcohol consumption, alcohol intake from beer and liquor and prostate cancer risk was found. Increased associations were found for alcohol from white wine and fortified wines compared to nondrinkers, but not for red wine. The RRs (95% CI) in the intake category of $\geqslant$15 g/day were 3.3 (1.2–9.2) and 2.3 (1.2–4.7), respectively, after additional adjustment for total alcohol intake. There was, however, no significant trend in risk. Alcohol intake was more strongly related with localized than with advanced prostate tumors.
Conclusion: Our results do not support an important role for alcohol in prostate cancer etiology. Nevertheless, for specific types of alcoholic beverages, particularly wines, a positive association was suggested which needs examination in further studies.

Introduction

Not much attention is given to alcohol consumption as a potential risk factor for prostate cancer in most reviews on this disease [1–5]. Nevertheless, when we searched the literature we found at least 14 cohort studies [6–19] and 23 case–control studies [20–42] in which alcohol consumption in relation to prostate cancer risk was investigated. In the majority of these studies, however, no extensive evaluation was made. For example, there were four cohort studies [6, 10, 13, 14] and 10 case–control studies [21, 22, 25–27, 33, 36, 38, 40, 41] in which some data on different types of alcoholic beverages were presented. In some studies it was suggested that alcohol consumption might be associated with prostate cancer etiology [11, 13, 14, 21, 22, 25, 26, 36, 40]. There were only three studies in which alcohol consumption was investigated in subgroups of aggressive or advanced prostate tumors [21, 25, 27]. Therefore, data on the hypothesis that environmental factors might be more strongly related to advanced prostate cancer are still sparse in regards to consumption of alcohol. We further investigated this relationship in the Netherlands Cohort Study (NLCS) on diet and cancer.

Materials and methods

The cohort

The study design has been described elsewhere [43]. In brief, the NLCS was initiated in September 1986. The

male cohort consists of 58,279 men who completed the questionnaire on usual diet, alcohol consumption, personal and family history of cancer, other risk factors for cancer, and demographic data. The case–cohort approach [44] was used for data processing and analysis: for calculation of cancer incidence rates, the number of cancer cases for the entire cohort was used as the numerator, while person-years at risk were estimated using a random male subcohort sample, which was sampled directly after identification of the total cohort. The male subcohort includes 1688 men. Follow-up for incidence of prostate cancer was established by computerized record linkage with all nine cancer registries in The Netherlands, and with the Dutch national database of pathology reports (PALGA) [45]. The subcohort has been followed up biennially for vital status information. Completeness of follow-up of cancer was at least 96% [46] and no subcohort members were lost to follow-up. After a follow-up period of 6.3 years (September 1986–December 1992), 704 incident, microscopically or histologically confirmed, primary prostate cancer cases were detected.

The questionnaire

The self-administered questionnaire has been described elsewhere [47]. Briefly, usual consumption of food and beverages during the year preceding the start of the study was assessed with a 150-item semiquantitative food-frequency questionnaire. Participants were asked to report their frequency of consumption of beer, red wine, white wine, sherry and other fortified wines, liqueurs and liquor (*e.g.* Dutch gin, brandy and whiskey). Categories ranged from "never or less than once per month" to "6–7 days per week" and information on the number of glasses drunk per consumption day was also requested. Daily alcohol consumption (ethanol in g/day) was calculated using the computerized Dutch food composition table [48]. The ethanol contents (per 100 g) used were: 4 g for beer, 10 g for red and white wine, 14 g for fortified wines, 17 g for liqueurs, and 29 g for liquor. The questionnaire has been validated against a 9-day diet record; the Spearman correlation coefficient for alcoholic beverages was 0.89 for all subjects and 0.85 for users of alcoholic beverages [47].

Data analysis

Questionnaire data were key-entered twice and processed for all incident cases in the cohort and for all subcohort members in a manner blinded with respect to case/subcohort status. This was done in order to minimize observer bias in coding and interpretation of the data. After excluding prevalent cancer cases other than skin cancer from the subcohort, 1630 men remained for analysis. Furthermore, subjects with incomplete alcohol data were also excluded. Alcohol data were considered incomplete when all questions on consumption frequency of alcoholic beverages were left blank and two questions on alcohol consumption pattern did not indicate that the subject was a nondrinker. These two questions concerned alcohol intake during the past week and 5 years previously [49, 50]. The results presented here are based on 680 incident prostate cancer cases and 1591 subcohort members for whom alcohol data were considered complete.

The associations between alcohol consumption and some potential confounding factors for prostate cancer were evaluated among men in the subcohort, by comparing the proportion of men with these risk factors across categories of alcohol consumption. Variables that were considered as potential confounders were age, prostate cancer in first-degree relatives (father and brothers), and socioeconomic status. Because in previous analyses no associations were observed between total vegetable and fruit consumption [51] and total energy and fat intake and prostate cancer risk [52], these factors were not considered as confounding factors. Rate ratios (RRs) and 95% confidence intervals (95% CI) were computed using the GLIM statistical package [53]. Exponentially distributed survival times were assumed in the follow-up period. Since standard software was not available, specific macros were developed to account for the additional variance introduced by using the subcohort instead of the entire cohort [54]. Tests for trend were based on likelihood ratio tests and two-sided p-values are used throughout this report.

Age-adjusted as well as multivariate-adjusted analyses were done for both categorized and continuous variables; in addition to the above-mentioned confounding factors, alcohol intake from specific types of alcoholic beverages was also adjusted for total alcohol intake. Cases detected during the first 2 years of follow-up were additionally excluded from analyses to evaluate whether preclinical symptoms might have influenced results. Analyses were also done in case subgroups of localized (T0–2, M0) and advanced (T3–4, M0; T0–4, M1) prostate tumors.

Results

The percentages of nondrinkers were 15.5 and 16.2, respectively, for subcohort members and cases. Among drinking men the mean total alcohol intake (SD) was 17.1 (16.6) g/day for subcohort members and 17.7 (15.9)

g/day for prostate cancer cases. Data on the association between alcohol consumption and some potential confounding factors among subcohort members are shown in Table 1. The proportion of older men was somewhat higher among nondrinkers compared to drinkers. Nondrinkers less often had a positive family history of prostate cancer and more often had a lower socioeconomic status than drinkers.

In Table 2, rate ratios of prostate cancer for both categorized and continuous variables of alcohol intake are shown. Total alcohol consumption was not related to prostate cancer risk in the NLCS. For men consuming 30 g alcohol per day or more the RR was 1.1 (95% CI: 0.8–1.6) compared to men who are nondrinkers. There was also no trend in risk. The RR for intake of alcohol from beer was decreased in the highest intake category (RR for $\geqslant$30 g/day *vs*. nondrinkers was 0.5, 95% CI: 0.2–1.3). In intermediate categories no associations were noted. For alcohol from liquor, no clear associations with prostate cancer risk were observed. For intake of alcohol from wine, a borderline significant increased risk was found for the highest *vs*. the lowest intake category (RR = 2.3, 95% CI: 1.0–5.3). In the intermediate-intake categories no increased risk was observed. The RR for the continuous variable was 1.1 (95% CI: 1.0–1.3) per 10 g increment.

In Table 3, alcohol intake is evaluated separately for different types of wine: red wine, white wine, fortified wines and liqueurs. Because of sparse data, the highest intake category comprised men consuming 15 g alcohol or more. For liqueurs there were only two exposure categories. No associations with risk of prostate cancer were found for intake of alcohol from red wine and liqueurs. For intake of alcohol from white wine, an increased risk was observed with higher consumption, but only in the highest intake category (RR = 3.3, 95% CI: 1.2–9.2). Also for intake of alcohol from fortified wines, only in the highest intake category was an increased risk found (RR = 2.3, 95% CI: 1.2–4.7) and no dose–response relationship was observed. The results shown in Tables 2 and 3 did not materially change after exclusion of cases detected in the first 2 years of follow-up (data not shown).

Alcohol intake was also evaluated in subgroups of localized and advanced prostate tumors and the results are shown in Table 4. The two highest categories of alcohol from beer (15–29 and $\geqslant$30 g/day) were combined to allow for a reasonable number of cases in the subgroup analyses. Furthermore, because the effect of alcohol from white wine and alcohol from fortified wines was similar in the overall analysis, these two sources of alcohol intake were combined in order to attain a reasonable number of cases. The number of cases for alcohol from liqueurs was not sufficient to conduct meaningful subgroup analyses. Overall, alcohol intake showed stronger associations with localized prostate tumors than with advanced prostate tumors. In the subgroup of localized prostate tumors, all RRs for total alcohol intake were above the null value, but only in the intake category of 0.1–4.9 g/day was a borderline significantly increased risk found (RR = 1.7, 95% CI: 1.0–2.6). No associations with advanced prostate tumors were found. Alcohol from beer showed no clear associations with risk of either

Table 1. Distribution of potential confounding factors for prostate cancer in male subcohort members with complete alcohol consumption data, Netherlands Cohort Study, 6.3 years of follow-up (1986–92)

Potential confounding variable	Percentage with risk factor		
	Nondrinkers (n = 246)	Drinkers	
		< 15 g/day (n = 767)	$\geqslant$ 15 g/day (n = 578)
Age (years)			
55–59	32.9	40.2	37.5
60–64	31.7	34.6	36.0
65–69	35.4	25.3	26.5
Family history of prostate cancer			
No	98.8	96.9	97.6
Yes	1.2	3.1	2.4
Socioeconomic status[1]			
Low	55.7	50.4	43.5
Medium	32.4	34.5	33.7
High	11.9	15.1	22.8

[1] Low is defined as primary school with/without lower vocational education, medium as secondary school or medium level vocational education, high as university or higher-level vocational education.

Table 2. Rate ratios (RRs) and 95% confidence intervals (95% CI) for prostate cancer according to intake of alcohol, Netherlands Cohort Study, 6.3 years of follow-up (1986–92)

Alcohol intake (g/day)	Age-adjusted		Multivariate adjusted[1]	
	No. of cases/person-years in subcohort	RR (95% CI)	No. of cases/person-years in subcohort	RR (95% CI)
Nondrinkers[2]	110/1440	1.00	109/1428	1.00
Total alcohol[3]				
0.1–4	143/1947	1.1 (0.8–1.5)	143/1931	1.1 (0.8–1.5)
5–14	161/2637	1.0 (0.7–1.3)	161/2624	0.9 (0.7–1.3)
15–29	162/2181	1.1 (0.8–1.5)	161/2162	1.1 (0.8–1.4)
$\geqslant 30$	104/1324	1.2 (0.9–1.7)	101/1324	1.1 (0.8–1.6)
		p-trend 0.37		*p*-trend 0.74
Continuous, 10 g increment		1.0 (1.0–1.1)		1.0 (1.0–1.1)
Alcohol from beer				
No beer	213/2621	1.1 (0.8–1.5)	212/2608	1.1 (0.8–1.5)
0.1–4	220/3376	1.0 (0.8–1.3)	218/3341	0.9 (0.7–1.3)
5–14	112/1594	1.2 (0.8–1.6)	111/1594	1.1 (0.7–1.6)
15–29	19/329	1.1 (0.6–2.0)	19/329	1.0 (0.5–2.0)
$\geqslant 30$	6/170	0.5 (0.2–1.3)	6/170	0.5 (0.2–1.3)
		p-trend 0.76		*p*-trend 0.48
Continuous, 10 g increment		0.9 (0.8–1.1)		0.9 (0.8–1.1)
Alcohol from wine				
No wine	220/3273	1.0 (0.8–1.4)	219/3239	1.1 (0.8–1.5)
0.1–4	199/2685	1.1 (0.8–1.5)	198/2679	1.1 (0.8–1.4)
5–14	91/1421	1.0 (0.7–1.4)	90/1415	0.9 (0.6–1.4)
15–29	40/575	1.2 (0.7–1.8)	39/575	1.1 (0.7–1.8)
$\geqslant 30$	20/135	2.3 (1.2–4.7)	20/135	2.3 (1.0–5.3)
		p-trend 0.12		*p*-trend 0.67
Continuous, 10 g increment		1.1 (1.0–1.3)		1.1 (1.0–1.3)
Alcohol from liquor				
No liquor	172/2616	1.1 (0.8–1.5)	172/2597	1.1 (0.8–1.5)
0.1–4	155/2211	1.1 (0.8–1.4)	154/2208	1.0 (0.7–1.4)
5–14	109/1595	1.0 (0.7–1.4)	109/1589	1.0 (0.7–1.4)
15–29	94/1149	1.1 (0.8–1.5)	92/1130	1.1 (0.7–1.6)
$\geqslant 30$	40/518	1.2 (0.7–1.9)	39/518	1.1 (0.6–2.0)
		p-trend 0.65		*p*-trend 0.96
Continuous, 10 g increment		1.0 (0.9–1.1)		1.0 (0.9–1.1)

[1] Adjusted for age, family history of prostate cancer, socioeconomic status, and total alcohol intake.
[2] Reference category.
[3] Not adjusted for total alcohol intake.

localized or advanced prostate tumors. For alcohol from wine, all RRs were increased in the subgroup of localized prostate tumors. Subjects consuming $\geqslant 30$ g alcohol per day from wine had a RR of 4.6 (95% CI: 1.6–13.4) compared to nondrinkers. Among advanced prostate tumors, only the RR in the highest intake category was increased (RR = 2.9, 95% CI: 1.0–8.5). In both subgroups, however, no trend in risk was observed. Although all RRs were increased for intake of alcohol from liquor in the localized prostate tumors subgroup, only one RR was statistically significant and a dose–response relationship was not observed (p-trend = 0.08). For advanced prostate tumors, no associations with intake of alcohol from liquor were apparent. No trend in risk was found for intake of alcohol from red wine in both subgroups. A borderline significant positive trend in risk was observed for the combined intake of alcohol from white wine and fortified wines among localized prostate tumors (p-trend = 0.06). Compared to nondrinkers, men with an intake of $\geqslant 15$ g/day had a RR of 3.6 (95% CI: 1.5–8.4). Among the advanced prostate tumor group, the effect estimate for the same contrast was 2.2 (95% CI: 1.0–5.2).

Table 3. Rate ratios (RRs) and 95% confidence intervals (95% CI) for prostate cancer according to intake of alcohol, Netherlands Cohort Study, 6.3 years of follow-up (1986–92)

Alcohol intake (g/day)	Age-adjusted		Multivariate adjusted[1]	
	No. of cases/person-years in subcohort	RR (95% CI)	No. of cases/person-years in subcohort	RR (95% CI)
Nondrinkers[2]	110/1440	1.00	109/1428	1.00
Alcohol from red wine				
No red wine	349/5071	1.0 (0.8–1.4)	347/5030	1.0 (0.8–1.4)
0.1–4	151/2178	1.1 (0.8–1.4)	150/2178	1.0 (0.7–1.3)
5–14	55/602	1.4 (0.9–2.2)	54/596	1.3 (0.8–2.0)
$\geqslant 15$	15/239	1.0 (0.5–1.8)	15/239	0.8 (0.4–1.7)
		p-trend 0.21		*p*-trend 1.00
Continuous, 5 g increment		1.0 (0.9–1.1)		1.0 (0.9–1.1)
Alcohol from white wine				
No white wine	362/5274	1.1 (0.8–1.4)	359/5233	1.1 (0.8–1.4)
0.1–4	180/2551	1.1 (0.8–1.4)	180/2545	1.0 (0.7–1.4)
5–14	20/226	1.3 (0.7–2.3)	19/226	1.2 (0.6–2.2)
$\geqslant 15$	8/38	3.4 (1.4–8.5)	8/38	3.3 (1.2–9.2)
		p-trend 0.13		*p*-trend 0.54
Continuous, 5 g increment		1.2 (1.0–1.5)		1.2 (1.0–1.5)
Alcohol from fortified wines				
No fortified wines	411/5772	1.1 (0.8–1.4)	408/5731	1.1 (0.8–1.5)
0.1–4	108/1599	1.0 (0.7–1.4)	108/1593	0.9 (0.6–1.3)
5–14	27/557	0.7 (0.4–1.2)	26/557	0.7 (0.4–1.1)
$\geqslant 15$	24/161	2.5 (1.3–4.7)	24/161	2.3 (1.2–4.7)
		p-trend 0.53		*p*-trend 0.77
Continuous, 5 g increment		1.1 (1.0–1.2)		1.1 (1.0–1.2)
Alcohol from liqueurs				
No liqueurs	511/7313	1.1 (0.8–1.4)	507/7266	1.0 (0.8–1.3)
0.1–4	52/669	1.2 (0.8–1.8)	52/669	1.1 (0.7–1.7)
$\geqslant 5$	7/107	1.2 (0.5–3.0)	7/107	1.2 (0.5–3.0)
		p-trend 0.37		*p*-trend 0.48
Continuous, 5 g increment		0.9 (0.6–1.4)		0.9 (0.6–1.5)

[1] Adjusted for age, family history of prostate cancer, socioeconomic status, and total alcohol intake.
[2] Reference category.

Discussion

In this study, we found no evidence that total alcohol consumption is related to the risk of developing prostate cancer. However, when specific types of alcohol were investigated, high intakes of alcohol from white wine and fortified wines were associated with increased risks. No clear associations existed between alcohol intake from beer, liquor, red wine, and liqueurs and prostate cancer risk. We found no evidence that consumption of alcohol is more related to advanced prostate tumors. On the contrary, alcohol intake showed mostly positive associations in the subgroup of localized prostate tumors.

An important strength of our study is the prospective design; therefore, recall bias is unlikely. Furthermore, selection bias due to loss to follow-up did not influence our results because of the high completeness of follow-up of cases and subcohort members in the NLCS [46, 55]. Another advantage is that the assessment of alcohol consumption in the NLCS allowed us to extensively evaluate a possible association with prostate cancer risk. Not only overall consumption of alcohol, but also different types of alcoholic beverages were investigated. Moreover, consumption of several types of alcoholic beverages was also evaluated within case subgroups based on tumor characterization. Misclassification of exposure is a possible limitation of our study. However, if misclassification has occurred, this is expected to be nondifferential and risk estimates are most likely biased towards the null value. Abstainers and ex-drinkers were not separated in our study, but were included in our reference category of nondrinkers. Ex-drinkers may differ in prostate cancer risk from abstainers; therefore

Table 4. Rate ratios (RRs) and 95% confidence intervals (95% CI) for prostate cancer according to intake of alcohol, in subgroups of localized and advanced prostate tumors, Netherlands Cohort Study, 6.3 years of follow-up (1986–92)

Alcohol intake (g/day)	No. of person-years in subcohort	Localized prostate tumors (T0–2, M0) n = 247		Advanced prostate tumors (T3–4, M0; T0–4, M1) n = 236	
		No. of cases	RR (95% CI)[1]	No. of cases	RR (95% CI)[1]
Nondrinkers[2]	1428	28	1.00	34	1.00
Total alcohol[3]					
0.1–4	1931	59	1.7 (1.0–2.6)	44	1.0 (0.6–1.6)
5–14	2624	55	1.1 (0.7–1.8)	63	1.1 (0.7–1.6)
15–29	2162	61	1.4 (0.9–2.3)	49	0.9 (0.6–1.5)
⩾ 30	1324	33	1.3 (0.8–2.2)	35	1.1 (0.7–1.8)
			p-trend 0.67		*p*-trend 0.94
Alcohol from beer					
No beer	2608	84	1.7 (1.1–2.8)	63	1.0 (0.6–1.6)
0.1–4	3341	82	1.4 (0.9–2.3)	81	1.1 (0.7–1.7)
5–14	1594	35	1.4 (0.8–2.5)	40	1.2 (0.7–2.1)
⩾ 15	499	7	1.0 (0.4–2.6)	7	0.7 (0.3–1.9)
			p-trend 1.00		*p*-trend 0.65
Alcohol from wine					
No wine	3239	87	1.9 (1.1–3.1)	65	1.0 (0.6–1.7)
0.1–4	2679	69	1.5 (0.9–2.5)	72	1.2 (0.8–1.9)
5–14	1415	33	1.5 (0.8–2.7)	32	1.0 (0.6–1.9)
15–29	575	11	1.4 (0.6–3.1)	14	1.2 (0.6–2.5)
⩾ 30	135	8	4.6 (1.6–13.4)	8	2.9 (1.0–8.5)
			p-trend 0.38		*p*-trend 0.25
Alcohol from liquor					
No liquor	2597	57	1.5 (0.9–2.5)	58	1.1 (0.7–1.7)
0.1–4	2208	63	1.7 (1.1–2.8)	58	1.2 (0.7–1.9)
5–14	1589	41	1.6 (0.9–2.8)	35	0.9 (0.5–1.6)
15–29	1130	33	1.8 (0.9–3.4)	25	0.9 (0.5–1.7)
⩾ 30	518	14	2.0 (0.8–5.3)	15	1.2 (0.5–3.0)
			p-trend 0.08		*p*-trend 0.78
Alcohol from red wine					
No red wine	5030	127	1.6 (1.0–2.5)	116	1.1 (0.7–1.8)
0.1–4	2178	60	1.6 (0.9–2.7)	46	0.9 (0.5–1.5)
5–14	596	16	1.6 (0.8–3.4)	24	1.7 (0.9–3.3)
⩾ 15	239	5	1.2 (0.4–3.7)	5	0.8 (0.3–2.5)
			p-trend 0.32		*p*-trend 0.70
Alcohol from white/fortified wine					
No white/fortified wine	4210	107	1.7 (1.1–2.8)	87	1.0 (0.7–1.7)
0.1–4	2804	70	1.5 (0.9–2.4)	73	1.1 (0.7–1.8)
5–14	785	19	1.6 (0.8–3.2)	20	1.2 (0.6–2.3)
⩾ 15	243	12	3.6 (1.5–8.4)	11	2.2 (1.0–5.2)
			p-trend 0.06		*p*-trend 0.12

[1] Adjusted for age, family history of prostate cancer, socioeconomic status, and total alcohol intake.
[2] Reference category.
[3] Not adjusted for total alcohol intake.

our estimated risks might be biased in either direction. Thus far, however, an association between alcohol and prostate cancer has not been established definitely and it is also not known whether or how the timing of alcohol consumption might play a role. Further studies are needed to evaluate this matter. We considered most of the factors that have been implied in prostate cancer etiology and factors showing an association with prostate cancer risk in the NLCS were included into the multivariate model. Thus, total energy and fat intake were not included and also vegetable and fruit consumption were not included. When multivariate analyses were conducted with inclusion of the above-mentioned factors, the rate ratios were not changed

essentially. Certainly, confounding by unmeasured or other unknown factors cannot be excluded.

In the majority of cohort [6–10, 12, 15–19] and case–control studies [20, 23, 24, 27, 29–31, 33–35, 37, 39, 41, 42] no association between total alcohol consumption and prostate cancer risk was found, and this was confirmed in the NLCS. In one cohort study in Japan, alcohol consumption was positively associated with prostate cancer risk and when specific alcoholic beverages were investigated, a significant positive association for consumption of shochu was noted [14]. In another cohort study alcohol abusers developed prostate cancer more often than expected [11]. In none of the cohort studies was a decreased risk observed. In case–control studies a few positive associations [21, 25, 26], as well as one inverse association [22] between total alcohol consumption and prostate cancer risk, were noted.

Although a nonsignificant decreased risk was suggested in the highest intake category of beer in our study, in the other exposure categories no association was found. Other cohort [6, 10, 13, 14] and case–control studies [25, 27, 33, 36, 38, 41] support a conclusion of no association between consumption of beer and risk of prostate cancer. There was one cohort study in which ex-users of beer showed an increased risk of prostate cancer mortality [13]. In three case–control studies, beer consumption increased prostate cancer risk [21, 26, 40] and in two of these studies also a significant trend in risk was reported [21, 26]. However, in one of these case–control studies other types of alcohol were also associated with an increased prostate cancer risk and therefore it was concluded that the association was due to alcohol and not due to some components of specific types of beverages [21].

No association was found between red wine and prostate cancer risk within the NLCS, but for consumption of white wine and fortified wines increased risks were observed at high intakes. Only in two other cohort studies was wine consumption evaluated, and no associations were noted [6, 10]. Also in most case–control studies no associations were found [21, 25, 27, 32, 33, 38, 41], although some positive [26, 40] and inverse associations [36] were indicated. Men consuming daily white wine or fortified wines might be a quite distinctive socioeconomic group of the highest level. Therefore, residual confounding by socioeconomic status or other factors related to socioeconomic status might be an explanation for our observed associations regarding alcohol intake from white wine and fortified wines. This explanation is further supported by the fact that, for intake of alcohol from beer, an inverse association was observed in the highest exposure category. Among older subjects, high intake of beer was more common in the lower than in the higher socioeconomic classes.

Consumption of liquor was, as in the NLCS, not associated with prostate cancer risk in most other epidemiological studies [6, 10, 13, 26–28, 33, 38, 40, 41]. Nevertheless, in three case–control studies a positive association was observed [21, 25, 36] and there was a significant trend in risk in one of these studies [21].

The biological pathway relating alcohol consumption to prostate cancer risk is largely unknown, but some mechanisms have been proposed to both explain an inverse as well as a positive association between alcohol consumption and prostate cancer risk. A decreased risk has been explained by the fact that ethanol has been found to decrease plasma testosterone levels [56], which might decrease prostate cancer risk [25, 26]. An increased risk of prostate cancer associated with alcohol consumption has been explained by metabolic activation of environmental nitrosamines by ethanol [21, 26]. Furthermore, alcohol contains contaminants that may be carcinogenic and the major metabolite of alcohol, acetaldehyde, is also known to be carcinogenic and teratogenic [21]. Immunodepression might also be a pathway through which tumor growth is stimulated by consumption of alcohol [57]. Indirect effects of alcohol consumption on prostate cancer risk could be nutrient displacement, malabsorption, liver effects and related pathology [21, 57]. A specific hypothesis concerning beer consumption that has been proposed is that the nitrosamine content of the beer in the past might be responsible for an increased risk of prostate cancer [26]. Finally, the observed positive associations of high white wine and fortified wine consumption with prostate cancer risk may be due to other unknown potential biological pathways (*e.g.* non-alcoholic constituents), or due to bias or confounding.

The hypothesis that environmental factors (alcohol consumption) are more strongly related to advanced prostate tumors was not confirmed in this investigation. On the contrary, for different types of alcoholic beverages, observed associations were most pronounced in the subgroup of localized prostate tumors. The stronger associations with localized rather than advanced prostate cancer might suggest a social class effect related to increased use of medical services among men with a higher socioeconomic status. However, this issue was separately investigated in the NLCS and no evidence for this explanation was found (submitted for publication). Results from other studies are also somewhat inconsistent and do not uniformly point into a direction of stronger associations with advanced prostate tumors [21, 25, 27].

In summary, although total alcohol consumption seems not to be related to prostate cancer risk, a positive effect of high intakes of specific types of

alcoholic beverages, *i.e.* white wine and fortified wines, cannot be excluded. Thus far, however, data from epidemiological studies on these types of wine are sparse. Also, because a possible biological pathway by which the observed effect can be explained is unknown, this topic deserves further investigation.

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